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Preeclampsia and Eclampsia: A consequence of Immunological maladaptation

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Abstract:*Preeclampsia (PE) is a pregnancy specific disorder occurring only in humans and high apescharacterized by development of hypertension, proteinuria and edema. Sometimes this disease progresses to multi organ dysfunction and further result in long term morbidities like chronic hypertension, diabetes, and obesity and remains the leading cause of maternal and perinatal mortality and morbidity. Currently immunological maladaptation, placental ischemia, oxidative stress, and genetic factors are suggested for etiopathogenisis. New advancements in immunology, immunohistochemistry, and human genomic study had given way for new insights in to the etiopathogenisis of this disease. Under the light of current scientific information, in this review, we analyzed the available evidence in support of immunological maladaptation, and made an attempt to explain both typical and atypical presentations of preeclampsia.*

Key Words: *Preeclampsia; Eclampsia; Immunological maladaptation.*

I. Introduction

Reproductive function progressively changed in the process of evolution in animal kingdom. Protozoans like amoeba multiply by binary fission. Earth worms are bisexual animals. In frogs fertilization and development of embryos occur outside the body of the mother, and on the surface of water. In birds the embryos stay inside the mother for a short period of time, and further development occur outside the mother in a shell of egg.In mammals, the hemochorial placenta carryout all the vital functions of respiration, excretion, and nutrition, and the fetus stays inside the uterus of the motherfor a long time, till it attains completion of functional maturity.This prolongedstay inside the mother results in deportation of fetal tissues/cells in to maternal circulation, and maternal cells in to fetal circulation[1], which results in certain immunologic problems.Deep endovascular invasion of trophoblast,which could be a consequence ofincreased nutritional demands of growing human fetal brain, is the specific character of human placentation when compared to lower mammals[2]. This deep trophoblast invasion, wide opens the maternal circulation for growing placenta and fetus, which mayalso permit larger entry of allogenic fetal cells in to mother. This could be the reason for preeclampsia representing a human specific disadvantage of reproduction compared to other mammals[1, 2].

Immunological interactions at fetomaternal interphase at the time of trophoblastic invasion: Atfetomaternal interphase the maternal immune system undergoes significant changes to accommodate the allogenic fetus. At the same time the maternal immune cells closely monitor the trophoblastic invasion and make efforts to protect the mother from unsafe and 'nonself' alloantigens of trophoblast. From fetal side, the trophoblast vehemently makes efforts to invade the endometrium by influencing the maternal immune system by different mechanisms to protect the growing (progeny) fetus[3] (Table.1).

All these interactions results in wide spectrum of outcomes. On one end of the spectrum, mother completely acceptsthe coceptus byproviding angiogenic environment, which results inflooding blood supplyto embryo permitting rapid growth of the fetus. This results indisappearance of uterine artery diastolic notch as early as 12 to 14 weeks. On the other end of the spectrum, maternal immune system completely reject the conceptus by creating an antiangiogenic environment, and cutting off blood supply, resulting in early spontaneous abortion. In between these two ends of spectrum, varying degrees of adaptations/mal-adaptations can occur resulting in varying clinical presentations like early onset PE,intra uterine growth retardation (IUGR), and late onset PE.This adaptation/ mal-adaptation process can occur not only between fetus and maternal immune system at fetomaternal

interphase, but also between maternal immune system and deported fetal tissues in different organ systems of the mother[1].

Factors operating from maternal side at fetomaternal interphase: The four main populationsof decidual leukocytes present in early-stage of pregnancyincludeuNK cells (uterine natural killer cells), macrophages, dendritic cells (DCs), and T-cells. Of these, the most abundant cells in order are, uNK cells (CD56+CD16− NK cells), macrophages (CD38+CD2±CD3−CD16−CD68+), and T CD3+ cells (CD8+and rare CD4+). B-cells are virtually undetected[4, 5]

Natural Killer (NK) cells: These cells are of two types based on the expression of surface markers CD56 and CD16.Cytotoxic type is predominant in peripheral circulation and they express CD56 dim CD16+ phenotype[6]. The cytokine type also known as uterine NK cells and express CD56 bright CD16- phenotype, andbecome predominant in the secretory phase of endometrium.This predominance continues in the fetomaternal interphase after the implantation of embryo[7, 8].Uterine NK cells regulate trophoblast invasion through the secretion of angiogenic growth factors, cytokines, andchemokines[9, 10].Angiogenic factors of uNK cells include vascular endothelial growth factor (VEGF), and placental growth factor (PlGF), andthe most abundant NKG5[10].Cytokines produced by uNK cells include interleukin 8 (IL8), interferon-inducible-protein-10 (IP-10), and the most synthesized chemokine, regulated upon activation normal T-cell expressed and secreted (RANTES) which triggers the migration of invasive trophoblast[10].

Uterine NK cells possessactivator or inhibitor receptors which belong to three main families. These are, type-C lectin family (CD94/NKG), the killer immunoglobulin-like receptor (KIR), and immunoglobulin like transcripts (ILT or the leukocyte immunoglobulin-like receptor)[11]. The effector function of NK cells depends on the fine tuning of these receptorsand they are considered activated when KIR receptors are constitutively expressed[6].This fine tuning receptor function further depends on the gene combinations between NK cells and extra villus trophoblast (EVT)[12].

KIR receptors are of 3 genotypes, KIR AA, AB, and BB. EVT express maternal and paternal HLA-C1 and HLA-C2ligands. The combinations of maternal KIR AA with fetal HLA C2 produce strong inhibitory signals which results in over expression ofanti-angiogenic factors like Soluble fms like tyrosine kinase-1(sFlt1), and Soluble Endoglin (s.Eng), and Transforming growth factor alpha (TGF alpha) by NK cells[12]. These factors act on invading trophoblast and produce endothelial dysfunction which results in implantation failure(Table.1)[13]. Likely these factors can also enter in to maternal circulation from extra villus area, and can register higher serum levels, as early as early second trimesterin women who are destined to develop PE[14].

On the other hand the combination of genotype KIR BB with HLA C1 of trophoblast results in activation of cytokine type NK cells. These cytokine type NK cells produce angiogenic factors like VEGF, PlGF, and TGF beta which produce anti-inflammatory and angiogenic state,facilitating trophoblastic invasion. This results in successful implantation and pregnancy(Table.1)[15].

Balance between pro- and anti-angiogenic factors: Angiogenesis is controlled by the balance between pro-angiogenic factors like VEGF, PlGF and anti-angiogenic factors such as sFft-1 and s.Eng.In normal pregnancy the balance between these factors achieve adequate angiogenesis in placenta[16]. In preeclampsia, recent studies have suggested that, excess of placenta-derived circulating factors, such as sFlt-1 and s.Eng disrupt the angiogenic balance in mother[17]. Soluble Flt1 binds to angiogenic proteins VEGF and PIGF, and blocks their actions on endothelium. Soluble Endoglin inhibits TGF-β1 from binding to the surface of its receptors on endothelium and diminishes nitric oxide-mediated endothelial signaling[15]. All these mechanisms results in endothelial dysfunction and clinical features of P. E.

Soluble Flt1 is produced by peripheral blood mononuclear cells: Michael HM et al. reported dysregulation of Flt1, resulting in over expression of sFlt1in peripheral blood mononuclear cellsof preeclamptic pregnant women[18]. This could result in peripheral endothelial dysfunction and the clinical manifestations of preeclampsia.

Soluble Flt1 is produced by deported trophoblastic cells: Recently several variants of sFlt1 have been discovered including sFlt1-14 which is expressed only in primates[19]. Soluble Flt1-14 expression increases dramatically in women with preeclampsia, and it is primarily produced by abnormal clusters of degenerative trophoblasts known as syncytial knots [20]. Soluble Flt1-14 is the predominant inhibiting protein capable of neutralizing the activity of VEGF on endothelium of distant organs implicated in preeclampsia such as kidney[20]. Soluble endoglin (s.Eng), a truncated form of endoglin CD105 is up regulated in preeclampsia which acts in concert with sFlt1 toproduce endothelial dysfunction(Table.1) [20, 21].

Antigen-presenting cell (APC): There are two types of APCs, one Dendritic cells (DC) and the other Macrophages. Immature DCs play a key role in initiating andmodulating the immune responses to induce tolerance at fetomaternal interphase facilitating the implantation of embryo(Table.1)[22, 23, and 24].APCs express major histocompatibility complexes (MHC) I and II on their surfaces and form complexes with foreign antigens. They process these antigens and present them to T cells, whichrecognize these complexes with their T-cell receptors.APCs which express MHC II can stimulate CD4+ (helper) T cells, and the cells which express MHC I can stimulate CD8+ (cytotoxic) T cells.

Immature DCs express highly specific and sensitive marker CD1a which mediate HLA independent antigen presentation pathway[25].In intra uterine and extra uterine pregnancies, the immature DC status prevails which has been related to the interaction with uNK cells[26, 27]. Mature DC status has been associated with implantation failure(Table.1)[28].

Heme Oxygenase-1 (HO-1) is a microsomal enzyme with anti-inflammatory, anti-apoptotic properties, and it is highly expressed by trophoblastic cells in earlypregnancy [29].HO-1 plays a key role in maintaining DCs in immature status in murine pregnancies.HO-1 blockade renders mature status for DCs which promotes activation of effector CD8+ T cells[29]. Pregnancy disorders like PE and IUGR are associated with diminished levels of HO-1 and impaired remodeling of maternal spiral arteries(Table.1) [30].

Macrophages: Macrophages form the next highest population at fetomaternal interphase after uNK cells and play a key role in feto-maternal tolerance[31, 32]. Functional maturation of macrophages leads to the formation of two types of phenotypes, M1or M2[5, 33]. M1type macrophages get polarized under the influence of proinflammatory environment[5]. These cells are classically activated Monocytes which participate in the progression of inflammation by producing Tumor necrotic factor alpha (TNF alpha) and IL12 which results in tissue destruction(Table.1)[33, 34].

In contrast M2 macrophages get polarized under the influence of anti-inflammatory cytokine (IL4, IL10) environment of Th2 cells(Table.1)[5]. These cells are alternatively activated Monocytes which enhance the production of anti-inflammatory cytokines, IL1 receptor antagonist,IL10, and TGF beta. This results in tissue repair and inhibition of inflammation[33, 34]. Polarization to M2 type cells in decidua of normal pregnancy indicates that their immunosuppressive activities are critical to maintain immunological homeostasis in pregnancy[5, 33].

M2 type cells aggregate around the spiral arteries and produce angiogenic factor VEGF and MMPs, and anti-inflammatory cytokineIL10. They alsoactivate and regulate the T cell activityby inhibitingCD8T-cell responses through E2 prostaglandin production.They also produce tryptophan metabolites that can abolish T-cell proliferation. They remove apoptotic cells and trophoblastic debris and supports vascular remodeling[31, 33].

Complement system: It is a part of innate immune system consists of number of small proteins found in the blood. These proteins are generally produced by liver, and complement the ability of antibodies and phagocytic cells to clear pathogens, immune complexes, necrotic and apoptotic cells by forming membrane attack complex[35, 36](MAC).Complement system get activated by three pathways. The classic pathway is triggered by antigen and antibody complexes. Alternative pathway is spontaneously and continuously activated and do not need a trigger. Lectin pathway is triggered by the binding of mannan-binding lectin (MBL) to the mannose residues on the surface of the cells or microorganism. All the pathways finally converge to generate C3 convertases which convert C3 in to active components C3a and C3b. C3b is the main effector that tags to 'non-self' cells which results in destruction and phagocytosis[36]. C3b also binds to C3 convertases to form C5 convertase, which transforms C5 into C5a and C5b, which is a powerful pro-inflammatory mediator[36].

In normal pregnancy the serum levels of complement components are high. But Syncytio-trophoblast, villus cytotrophoblast, and EVT express three regulatory proteins of complement. These include Decay accelerating factor (DAF), Membrane co factor protein (MCP) and CD59 which prevents the formation membrane attack complex (MAC) and subsequent lysis of trophoblast cells, which results in successful continuation of pregnancy[36](Table.1).

Excessive activation of complement particularly enhanced synthesis of C5a is associated with preeclampsia, preterm labor and recurrent abortion. This excessive C5a synthesis induces sFlt-1 synthesis, which blocks the actions of VEGF and PlGF on endothelium, which are crucial factors for normal placental development and successful pregnancy[36](Table.1).Higher plasma levels of C3a had been observed before 20wks gestation in women who are destined to develop PE at a later age of gestation[37].

Mannose binding lectin (MBL): Mannose binding lectin is aprotein produced by liver as a response to infection and it is instrumental in innate immunity. This protein belongs to the class of collectins in C type super family and recognizes carbohydrate molecules on the surface of microorganisms. MBL binding to the surface of microorganism, results in activation of lectin path way of compliment. MBL also binds on to the surface of senescent, apoptotic and necrotic cells and enhances phagocytosis. Women with PE show higher median plasma levels of MBL when compared to uncomplicated pregnant women[38]. Polymorphisms involving MBL synthesis result in reduction of functional efficacy of MBL which protect against PE(Table.1)[35].

Complement protein C1q: C1q is another component of complement protein, plays an important role in trophoblast migration and vascular remodeling[39]. The decidual endothelial cells (DEC) covering spiral arteries acquire the capacity to produce C1q. This protein binds to the cell surface and forms a direct physical link between DECs and EVT, and enhances the trophoblast invasion and spiral artery remodeling [35]. C1q deficiency in pregnant rats results in clinical picture similar to that of PE[39].

Ficolins: These are soluble molecules of innate immune system.They recognize carbohydrate molecules on the surface of pathogenic microbes, apoptotic and necrotic cells and activate the lectin pathway of complement system which enhances the process ofopsonophagocytosis. Plasma Ficolin-2 levels are observed to be low in women with preeclampsia when compared to healthy pregnant women(Table.1). Diminished ficolin-2 levels results in reduced clearance and accumulationof deported trophoblast material derived from preeclamptic placenta[40].

Fas- ligand (Fas-L): Fas-L is a transmembrane protein expressed by decidual macrophages, and EVT. This protein binds to Fas receptor baring activated CD8+ T cells (cytotoxic) and triggers apoptosis[41, 13]. This results in reduction of deleterious maternal immune responses against allogenic embryo. It has been recently reported that the Fas-L A-670G polymorphism is associated with increased risk for preeclampsia(Table.1)[42].

Toll like receptors (TLR): These are a class of proteins that play a vital role in the innate immunity. These are pattern recognizing receptors expressed by the cells of innate immune system, recognizes the pathogen associated molecular patterns (PAMPs) on microbes[43]. Cultured cells isolated from term placenta, both cytotrophoblast and syncytiotrophoblast cells have been shown to express TLR2, TLR3, TLR4, TLR5 and TLR6 [44]. An immune response mediated through TLRs expressed on trophoblast cells, has been postulated to contribute to the pathogenesis of a variety of pregnancy complications like abortion, preterm labor and preeclampsia(Table.1) [45].E. Nakada et al. in their study reported, stimulation of TLRs, in particular TLR3, induced sFlt-1 up regulation in trophoblasts via the intense signaling pathways of NF-kB and IRF[16].

Indole amine 2, 3-dioxygenase (IDO): Indole amine 2, 3-dioxygenase (IDO) is an enzyme that catabolizes tryptophan. This enzyme is expressed by villus and extra villus trophoblast, and inhibits maternal T-cell activation by deprivation of tryptophan in T-cells.This tryptophan-catabolizing enzyme by this waycan provide protection to the fetus from maternal T cells [11, 46] (Table.1).

HLA antigenicity of trophoblast: The vast majority of the trophoblast that comes in contact with maternal tissues does not possess the antigenic determinants required for T-cell activation. This helps to prevent the potential maternal antifetal rejection. The syncytiotrophoblast which is the main trophoblast that come into contact with the maternal immune system lacks classic class I and II HLA antigens. EVT, an invasive phenotype forms columns of cells that invade the maternal decidua and replace the endothelium of spiral arteries. EVT expresses a single class I HLA expression pattern with non-polymorphic molecules, which include HLA-E, -F, -G, and -C[15]. Of all HLA class I molecules expressed by EVT, only HLA-C displays the variability required to constitute a fetal alloantigen, and it is recognized by maternal uNK cells through their KIR receptors[15].

HLA G plays a crucial role in maternal tolerance for fetal allograft. HLA G expression in EVT is observed throughout the period of pregnancy, and induces cytotoxic T (CD8 +T) cell apoptosis through Fas-Ligands[11, 15]. A leader peptide of HLA G forms a complex with HLA E on the surface of trophoblast cells that binds to the CD94/NKG2 receptors of uNK cells which results in inhibition of cytotoxic NK cells[11].

Syncytio trophoblast cells that come in contact with maternal immune cells do not possess HLA I & II antigens[15]. But the trophoblastic debris, circulating in maternal blood expresses intra cellular fetal HLA-DRantigenswhich can trigger immunological mal-adaptation(Table.1)[15]. It has been postulated that the premature DCs acting as APCs catch these antigens and induce peripheral tolerance through induction of Treg Cells[15] (Table.1). The circulating Treg cells start increasing from first trimester and reach high levels in second

Table.1:Feto-maternal tolerance

Fetomaternal adaptation in normal pregnancy	Fetomaternal maladaptation in preeclamptic pregnancy
Gene combinations like KIR BB of NK cells with HLA G, HLA C1 of trophoblast, results in predominance and activation of cytokine type NK cells at feto-maternal interphase in early pregnancy. These cells produce angiogenic factors VEGF, PlGF, TGF beta and chemokines like RANTES. Results in anti-inflammatory & angiogenic state and regulation of trophoblastic invasion and successful implantation.	The gene combinations of KIR AA of NK cells with trophoblastic HLA C2 produce strong inhibitory signals. Persistence of predominance of Cytotoxic type of NK cells at feto-maternal interphase in early pregnancy. Over expression of anti-angiogenic factors sFlt1, s.Eng, and TGF alpha by NK cells. Results in endothelial dysfunction and implantation failure, or preeclampsia at later stages of pregnancy.
The trophoblastic debris circulating in maternal blood expresses intra cellular fetal HLA- DR antigens. The premature DCs acting as APCs catch these antigens and induce peripheral tolerance through induction of Treg cells.	Over expression of sFlt1in peripheral blood mononuclear cells, and excessive production of sFlt1-14 by circulating syncytial knots, and up regulation of s.Eng, results in peripheral endothelial dysfunction and the clinical features of P.E
Immature Dendritic Cell status prevails in normal pregnancy. Induces tolerance at feto-maternal interphase and facilitates the implantation of embryo.	Mature Dendritic Cell status is associated with implantation failure and adverse pregnancy out comes like preeclampsia.
Enzyme Heme Oxygenase-1 (HO-1) which is expressed by trophoblastic cells in early pregnancy maintains immature status inDendritic Cells.	Pregnancy disorders likepreeclampsia and fetal growth restriction are associated with diminished levels of Heme Oxygenase-1.
Macrophages get polarized to M2 type under the influence of anti-inflammatory cytokine (IL4, IL10) environment of Th2 cells. These cells enhance the production of anti-inflammatory cytokines, IL1 receptor antagonist, IL10, and TGF beta, and produce VEGF and MMPs.	Macrophages get polarized to M1 type under the influence of pro inflammatory environment. These cells participate in the progression of inflammation by producing TNF alpha and IL12 which results in tissue destruction.
Trophoblast express three regulatory proteins of complement, DAF, MCP, and CD59 which prevents the formation of MAC and subsequent lysis of trophoblast	Excessive activation and enhanced synthesis of complement C5a is associated with preeclampsia, preterm labor and recurrent pregnancy loss. This excessive C5a synthesis induces sFlt-1 synthesis.
Fas-L, a transmembrane protein expressed by decidual macrophages, and fetal extra villous trophoblast, binds to Fas receptor baring activated CD8+ T cells (cytotoxic) and triggers apoptosis.	Fas-L A-670G polymorphism is associated with increased risk for preeclampsia.
In normal pregnancy, Th2 preponderance, low Th1/Th2 ratio, low peripheral blood levels of mononuclear cell product IL12 are observed. Raised levels of chemokine RANTES, which modulates alloantigen specific T cell responses is observed	In preeclamptic pregnancy Th1 predominance, high Th1/Th2 ratio, high serum IL2/IL4, and IFNg/IL4 ratios, elevated circulating pro-inflammatory cytokines IL6, TNF alpha, and raised chemokines IL8, IP10, MCP-1, and raised adhesion molecules ICAM and VCAM-1 are observed.
Treg cells regulate the balance between CD4+T cells and CD8 T cells, which results in feto maternal tolerance and continuation of pregnancy	The frequency of conventional Treg cells (CD4+CD25high Foxp3+) and non-conventional Treg cells (CD4+CD25- Foxp3+) diminish in peripheral blood of women with P.E
The enzyme Indole amine 2, 3-dioxygenase (IDO) expressed by trophoblast, depletes tryptophan in maternal T cells which helps to protect the fetus from maternal T cells.	Women with preeclampsia show higher median plasma levels of MBL. Polymorphisms in MBL synthesis result in reduction of efficacy of MBL which protects against preeclampsia.
The functions of B cell compartment which produce antibodies against antigens is partially suppressed during normal pregnancy	CD19+CD5+B-1a B cell which are a major source of natural and poly reactive autoantibodies are observed to increase in peripheral blood and placentae of women with preeclampsia
	Plasma Ficolin-2 levels are reduced in preeclampsia which results in reduced clearance and accumulation of deported trophoblast material
	Significant increase in the TLR-4 protein expression in trophoblast was observed in preeclamptic women.

Table 1: Feto-maternal tolerance: The adaptation/ mal-adaptation processes between fetus and maternal immune system in normal pregnancy and preeclampsia. APC: Antigen presenting cell; DAF: Decay accelerating factor; Fas-L: Fas ligand; **HLA:** Human leucocyte antigen; ICAM: Intra cellular adhesion molecule; IFN: Interferon; IL: Interleukin; IP10: Interferon inducible protein 10.KIR: Killer immunoglobulin like receptor; MBL: Mannose-binding lectin; MMP: Matrix Metalloproteinase MCP: Monocyte chemo-attractant protein; NK cells: Natural killer cells; PlGF: Placental growth factor; RANTES: Regulated on Activation, Normal T cell Expressed and Secreted; sFlt1: Soluble fms-like tyrosine kinase-1; s. Eng: Soluble endoglin; Th: T- helper cell; TLR: Toll like Receptor; TGF: Transforming growth factor; TNF: Tumor necrosis factor; Treg cells: regulatory T cells; VCAM: Vascular cell adhesion molecule; VEGF: Vascular endothelial growth factor.

trimester. Their levels start declining in third trimester and further continue to decline in postpartum [47]. This could be one of the reasons for higher incidence of preeclampsia in third trimester.

Maternal systemic immunological modulation in normal pregnancy and PE: Th lymphocytes are of twotypes. Th1 cells are associated with cell mediated immunity, and Th2 cells are associated with humeral immunity against extra cellular pathogens. Th2 cells produce IL4, IL5, IL6, IL9, IL10, IL13 and they repress the function of phagocytic cells. Th1 cells synthesize interferon gamma (IFNg), IL2, TNF alpha, and they trigger cell mediated immunity and phagocyte dependent inflammation[48]. It has been observed, Th2 cell predominance in the decidua of endometrium in secretory phase of menstrual cycle.If conception occurs,this predominance continues further in to normal pregnancy. A ten-fold increase in Th2 cells was observedwhen compared to Th1 cells in normal healthy pregnant women[49, 50].

Th2 preponderance in normal pregnancy shifts to Th1 dominance in preeclamptic pregnancy. Low Th1/Th2 ratio of normal pregnancy shifts to high Th1/Th2 ratio in women with preeclampsia[51].Increase inserum IL2/IL4, and IFNg/IL4 ratios, which represent a change towards Th1 immunity has been observed in preeclampsia[51].Elevated levels of circulating pro-inflammatory cytokines IL6, TNF alpha, chemokines IL8, IP10, MCP-1, and adhesion molecules ICAM (intra cellular adhesion molecule), and VCAM-1 (vascular cell adhesion molecule-1) are observed in preeclamptic pregnancies when compared to normal healthy pregnancies(Table.1)[51].Also increased levels of IP10, MCP-1, ICAM, andVCAM-1, positively correlate with severity of hypertension, and withparameters of hepatic and renal dysfunction [51]. Peripheral blood levels of mononuclear cell product IL12, which induces Th1 responses, is high in preeclamptic pregnancy when compared to normal pregnancy[52]. All these changes results in shifting of anti-inflammatory environment of normal pregnancy to pro-inflammatory environment in preeclamptic pregnancy.

A major chemokine RANTES is secreted by cytokine type of NK cells and trophoblast. This chemokine can act as a modulator of alloantigen specific T cell responses in healthy pregnancy[5]. Successful pregnancies are associated with increased serum levels of RANTES. Their levels are observed to be low in women with recurrent pregnancy loss [53]. It has been reported, RANTES specifically suppress alloantigen activated maternal T cells in vitro studies[5]. This indicates that RANTES might play an important role in maternal tolerogenic immune responses to allow trophoblast cell survival and migration[5].

Role of T regulatory cells (Treg cells) in fetomaternal adaptation: T regulatory cells are component of immune system that suppresses the immunological responses for 'nonself'cells. This is an important inbuilt self-check system present in the immune system to prevent excessive immunological reactionswhich are developed against invading organisms after their elimination[54]. Treg cells are involved in preventing autoimmune reactions for self-cells[55].Treg cells regulate the balance between CD4+ T cells and CD8 T cells, which results in feto maternal tolerance and continuation of pregnancy(Table.1)[15].$CD4^+$ T cells are commonly divided in to conventional T helper (Th1 and Th2) cells, and regulatory T cells (Treg cells). Th (helper) cells control adaptation immunity against pathogens and cancer cells by activating other immune cells[55]. Treg cells are $CD4^+$ T cells which suppress the potentially deleterious effects of Th cells[55].

Treg cells (CD4+CD25+Fox p3+) express transcriptional regulatory protein fork head box P3 (FOXP3) which is required for their development and function[56]. Decidual Treg cells express either high levels of CD25 ($CD4+CD25^{bright}$ Foxp3), or low levels of CD25 ($CD4+CD25^{dim}$ Foxp3) protein[57]. Decidual Treg cells which express $CD4+CD25^{bright}$ Foxp3 contribute to the maternal immune tolerance for fetal antigens. These cells are abundant in deciduas of early human pregnancy and express high levels of cytotoxic T lymphocyte activated antigen-4 (CTLA4) and prevent the proliferation of autologous CD4+CD25- T-cells.

Proportion of decidual $CD4+CD25^{bright}$ Treg cells is low in spontaneous abortion than in induced abortion[58].The frequency of conventional $CD4+CD25^{high}$ Foxp3+ Treg cells and non-conventional CD4+CD25-Foxp3+ Treg cells diminish in peripheral blood of women with preeclampsia when compared to normal healthy pregnant women (Table.1)[59].

Maternal antibodies against fetal antigens: The roles of innate and cell-mediated immunity, including natural killer cells, T helper type 1 or 2 (Th1/Th2) cells and regulatory T cells (T_{reg}) are well documented in pregnancy[60, 61]. B cells, which are known primarily for antibody production, also act as antigen-presenting cells, and regulate the innate and adaptive immune systems[62, 63]. B cells provide a vital source of antibody-mediated protective immunity for the mother and her baby during both pregnancy and lactation[64]. However production of some deleterious autoantibodies by auto reactive maternal B cells can contribute directly to adverse pregnancy outcomes[65]. $CD19^+CD5^+$B-1a B cells are a major source of natural and poly reactive autoantibodies. Recent

studies reported adramatic increase in B cell ($CD19^{+}CD5^{+}$B-1a)count in peripheral blood and placentae of pre-eclamptic women when compared to normal pregnant controls[66].

Normal pregnancy can induce loss of responsiveness in B cells for mitogens and infectious agents in both human and animal studies[67, 68]. These studies suggest, overall partial suppression of B cell compartment and its functions during normal human pregnancy(Table.1). This suppression is believed to enable immune tolerance for allogenic fetus.

Observations relevant to support the concept of immunological maladaptation:

Similarities between preeclampsia and other immunological disorders: Atypical presentation is the hallmark of immunological disorders. If we observe immunological disorders like SLE, scleroderma, rheumatic fever, neuro syphilis, all of them are atypical in their clinical presentations. They need multiple criteria(major, minor or their combinations) for their diagnosis. Similar atypical presentations are also observed in PE.

Concept of multiple systemic involvements with unequal severity: In all these immune disorders, multiple systems are involvedbut their involvement is not of same severity. One of the systems might be leading and other organ systems might be lagging behind with different degrees of severity of involvement. In this process, some of the systems might not be involved or skipping.Similar pattern of multi systemic involvement and skipping of involvement of systems can also be seen in preeclampsia.

Many studies have reported 40% of women with eclampsia have seizures at normal blood pressure and without proteinuria[69]. Gestational hypertension may result due to the involvement of vascular system without the significant involvement of other systems. Isolated IUGR may also be due to the involvement of utero-placental system in a similar fashion.Many authors reported abnormal Sonographic liver findings consistent with sub-capsular hematoma prior to the clinical and laboratory findings of preeclampsia[70, 71]. Even HELP syndrome is classified as partial HELLP and full HELLP syndrome based on the number of abnormalities involved[72]. All these observations indicate the atypical nature of the disease, which is the hallmark of immunological disorders.

In a preeclamptic woman with multisystem involvement with unequal severity, if pregnancy continues further, the dysfunctions in all organ systems progress further and results in multi organ dysfunction syndrome which leads to maternal death[73]. There is every need to consider this fulminant disease as similar to that of a running mismatched blood transfusion.Timely termination of pregnancy helps to prevent maternal death.

Eclamptic convulsions without the raise in blood pressure: Blood Brain Barrier (BBB) function is carried out by cerebral vascular endothelial cells. High electrical resistance tight junctions of endothelial cellscan be rapidly modulated by signaling path ways which affect the organization ofendothelial cell actin cytoskeletal structure[74, 75]. Similarly, trans-cellulartransport has been shown tobe regulated by mediators such as VEGFand otherinflammatory mediators[76,77]. The unique morphological feature of this endothelium is to prevent the passage of solutes and ions from blood in to brain tissues. In addition the cerebral endothelial cells have very low rate of hydraulic conductivity, which limit the passage of water in to the brain tissue in response to raised hydraulic pressure[78]. This prevents the edema formation in brain in normal health.

The endothelial dysfunction, the hallmark of preeclampsia can result in disruption of BBB function of cerebral endothelial cells resulting in leaking of water, albumin, and other damaging proteins in to brain parenchyma which can lead to vasogenic edema and convulsions[79, 80].Asconvulsions can occur in 40% of women without the elevation of blood pressure[81], this endothelial dysfunctioncould be due to the circulating factors,rather than merelysecondary to the rise in blood pressure. Vasospasm might also be occurring locally which can further aggravate the endothelial dysfunction.

Animal studies reported that, plasma samples from women with severe PE could increase the BBB permeability when compared to the plasma samples from normal healthy pregnant women. This effect could be completely blocked by nonselective VEGF receptor tyrosine kinase inhibitor[82]. These studies suggest that, there are circulating factors in preeclampsia that can increase the permeability of BBB, independent of inherent changes in barrier function[81].

Renal dysfunction without the raise in blood pressure: In pre-eclampsia, inhibition of VEGF- and TGF-beta signaling pathways leads to swelling and loss of fenestrae of glomerular endothelium, which results in reduction of glomerular filtration rate. Also, endothelial glycocalyx an impressive barrier which covers glomerular

endothelial cells and their fenestrae, get disrupted resulting in leaking of albumin and other proteins in to the urine[83].Takako Ohmaru et.alreported only renal dysfunction with massive albuminuria, and with elevated serum levels of sFlt1 and s.Eng, and without theraise in blood pressure and involvement of other systems[84].

Sonographic liver changes prior to clinical signs of preeclampsia: Many authors reported abnormal Sonographic liver findings consistent with sub-capsular hematoma prior to the clinical and laboratory findings of preeclampsia.Later these women developed severe pre-eclampsia and HELLP syndrome within 24 hours. In these women liver dysfunction was leading, which was later followed by dysfunction in other organ systems[70, 71]

Newborns do not express clinical features of preeclampsia: In a case of preeclampsia, both mother and baby stay in the same pathophysiological environment.But, we see only mother suffering from clinical features of preeclampsia but not the newborn baby. Deportation of cells occurs from fetus to mother, and also from mother to fetus[1]. In fetus, KIR expression in NK cells for both 'self and non-self' cells is blunted and prevents immune responses for allogenic maternal cells. This could be the reason for the fetus not manifesting the disease[85], and this supports the concept of immunological basis for pathogenesis.

Preeclampsia, a human specific disorder: Deep endovascular invasion of trophoblast, which could be a consequence of increased nutritional demands of growing human fetal brain, is the specific character of human placentation when compared to lower mammals[2]. This can also permit larger deportation of fetal 'non-self' cells in to maternal circulation.In highly evolved animals like higher apes and human beings, more effective immunological mechanisms might have evolved to recognize and reject 'non self' cells and pathogenic organisms as a better defense against disease. In this process of evolution, preeclampsia might have resulted as a human specific disadvantage of reproduction[86].

During the first trimester of pregnancy, most DCs express DC-specific adhesion receptor DC-SIGN (dendritic cell-specific ICAM grabbing nonintegrin, classified as CD209) in endometrium. DC-SIGN is also expressed by immature DC cells in peripheral tissues[25]. In fact the DC-SIGN expression at the feto- maternal interface with selective distribution in the rhesus macaque has been reported as an early response by the primate maternal immune system to the implanting embryo[87]. This DC-SIGN could have evolved to counter the effective human immune system to facilitate feto maternal tolerance.

Lower incidence of PE in subsequent pregnancies: HLA DR antigens expressed on sperm might induce HLA II antigen specific tolerance in mother. Treg cells play a central role in inducing and maintaining this process of fetomaternal tolerance which results in success of implantation [88]. Murine models have shown that Treg cells are activated by male antigens of seminal fluid, which results in accumulation of these cells in uterus even prior to the implantation of embryo[89, 15]. For the same reason prior exposure to semen in women with the same partner would reduce the risk for development of preeclampsia. With donor sperm, the risk for development of preeclampsia increases as there is no prior exposure. In ED pregnancies the complete fetal gnome is allogenic to mother, and prior exposure to semen is also not present. In these pregnancies the incidence of women developing preeclampsia is as high as 33%[15].The memory T cells of sperm antigens progressively decrease after delivery. But seminal priming may maintain their number at a certain level. In subsequent pregnancies with the same partner, the memory T cells rapidly increase in number which reduces the risk for development of preeclampsia. This protective effect against preeclampsia in multiparity would be lost with the change of partner[15]. The seminal priming effect of memory T cells progressively decreases after last delivery, and reach minimum level at more than 10 years. If the interval between two pregnancies is too long, some of these women may not achieve adequate tolerance andmay develop preeclampsia[15].

Preeclampsia does not occur before 20wks of gestation: Secondary trophoblastic invasion begins at 11 to 12wks, and completes by around 24wks of gestation. Delayed secondary trophoblastic invasion is a predictor of preeclampsia and IUGR [90].This secondary invasion results in wider opening of maternal circulation for trophoblast, which also facilitates increased deportation of fetal cells in to maternal circulation. In some women, thesecondary trophoblastic invasion completes as early as 11 to 14wks resulting in disappearance of uterine artery diastolic notch. In such women the incidence of developing PE in later pregnancy is very low[93, 91,92]. These pregnancies could be pregnancies with well-matched fetuses, and the deported fetal tissues cannot trigger larger number of mismatches in mother. For the same reason these women might not be developing PE in later course of pregnancy.

The delayed secondary trophoblastic invasion could itself be due to the immunological resistance offered by the mother for a 'not well matched' embryo[93, 94]. When delayed invasion completes beyond 24wks, increased deportation of not well matched fetal tissues cannot occur before 20wks. This could be the reason for PE not

developing before 20wks.In delayed invasion the mismatched tissues enter in to maternal circulation beyond 24wks. This could be the reason for higher incidence of PE occurring in late second trimester and third trimester.

Preeclampsia can occur before 20wks of gestation in molar pregnancy: Preeclampsia can occur in women with molar pregnancieseven before 20wks gestation [95]. By nature the molar tissue is highly invasive, and can enter in to maternal circulation even before 20wks.As genetic and chromosomal abnormalities with molar pregnancies arecommon, these tissues can trigger increased number of mismatches with maternal immune cells. This can result in immunological mal-adaptation and preeclampsia even before 20wks.

Incidence of PE is high in multifetal pregnancy: In multifetal pregnancy,deportation of different genetic materials in to maternal circulation can occur from different fetuses arising from different zygotes. This can result inincreased number of mismatches between deported cells and maternal immune system. This could beone of the main reasons for higher incidence of PE in multifetal pregnancies. Many authors reported disappearance of clinical features of preeclampsia with the demise of single fetus in twin pregnancies. In these cases the dead fetus could be the mismatched fetus and its demise might have resulted in remission of the disease[96, 97, 98, and 99]

Preeclampsia can occur in postpartum period: Failure of secondary trophoblastic invasion, placental ischemia[100], and oxidative stress are common observations in preeclampsia. But these observationswhether cause or effect for development of preeclampsia is an unsettled issue. Many cases of preeclampsia developing 48hrs after delivery,and also many cases of HELLP syndrome occurring up to 7days after delivery had been reported[101]. In such cases there is no placenta, no failure of secondary trophoblastic invasion, and no placental ischemia is present. But these woman manifests preeclampsia. Deported trophoblastic cells and micro chimeric fetal DNA persists for a long time in maternal systems even after delivery[1]. These cells may activate the maternal immune system, as the immunomodulatory effect of fetus and placenta mighthave gone off with their exit after delivery.In these cases,faster remission of clinical features of PE andHELLP syndrome was reported in women who received corticosteroids than the women who did not receive steroids. This further supports the concept of immunological basis for this disease[102].

Severe pre-eclampsia and HELLP syndrome following blunt abdominal trauma: V.J. Faber et.al reported, manifestation of severe PE and HELLP syndrome within 24 h after sustaining blunt abdominal injury in a woman at 27+wks gestation with no clinical features of preeclampsia. On investigation, massive fetal blood cells were observed in maternal circulation by Kleihauer-Btkey test [103, 104]. Sudden entry of large quantities of fetal tissues in to maternal circulation might have resulted in an excessive innate immune response triggering fulminant immuno-inflammation, i.e., severe preeclampsia and HELLP syndrome.

In our antenatal clinics we routinely monitor blood pressure, albuminuria, wait gain and edema. Also we look for clinical features of imminent eclampsia. But we do not check for liver dysfunction and coagulation dysfunction. As we have mentioned earlier, these dysfunctions can be present without the clinical features of involvement of other systems[72]. In these women, unpredictable heavy bleeding can occur during caesarean section or after vaginal delivery which may sometimes prove fatal.

It appears that, fetomaternal adaptation mechanisms start operating from the moment of implantation of embryo and continue to operate throughout pregnancy and also for few weeks postpartum. Also it appears that these mechanisms may break down at any time for different reasons and the mother may manifest preeclampsia.

II. Conclusion

Human feto-maternal adaptation is one of the great secrets of nature which involves multiple pathways, and holds the key for etiopathogenisis of preeclampsia. As there is no other way than the human fetus to grow inside the mother, the immunological reactions to alloantigens of the fetus in mother cannot be avoided, and hence preeclampsia cannot be preventable.Further research should be directed to develop techniques to boost the fetomaternal tolerance mechanisms to continue pregnancies to near viability of fetus. Treatments with monoclonal antibodies against sFlt-1, and ICAM had been attempted in animal studies to find out better therapeutic options[105, 106].Techniques should also be developed to attain completion or near completion offunctional maturityof fetus, at earlier gestational ages to avoid deleterious effect of preeclampsia on fetus and mother. The concept of 'Individualised term for each fetus, based on amniotic fluid optical density' is of help in this regard [107]. Cost effective NICU techniques should also bedeveloped to salvage many premature babies delivered due to preeclampsia.

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